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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MORRISON & FOERSTER LLP 425 MARKET STREET SAN FRANCISCO, CA 94105-2482			EXAMINER GOON, SCARLETT Y	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/573,335	Applicant(s) AGVALD ET AL.	
	Examiner SCARLETT GOON	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 41-75 is/are pending in the application.
- 4a) Of the above claim(s) 42-51, 53, 57-64, 67, 69, 71 and 73 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 41, 52, 55, 56, 65, 66, 68, 70, 72 and 74 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>24 March 2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The preliminary amendment filed on 24 March 2006 in which claims 1-40 were cancelled, and claims 41-75 were newly added, is again acknowledged.

Claims 41-75 are pending in the instant application.

Priority

This application is a National Stage entry of PCT/SE2005/001336 filed on 14 September 2005 and claims priority to Sweden foreign application 0402221-6 filed on 14 September 2004. A certified copy of the foreign priority document in English has been received.

Information Disclosure Statement

The information disclosure statement (IDS) dated 24 March 2006 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Election/Restrictions

Applicant's election with traverse of Group II, claims 41, 52-60, 65, 66, 68, 70, 72 and 74, drawn to a composition for the delivery of gaseous nitric oxide, comprising an alcohol compound in the reply filed on 5 March 2009 is acknowledged. The traversal is on the ground(s) that a search of all groups would not present an undue burden on the Office. This is not found persuasive because under PCT Rule 13.1, restriction for

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examination purposes is proper if there is a lack of unity of inventions. As indicated on pages 3-4 of the Office Action dated 5 January 2009, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The common technical feature in the different groups is a composition for the delivery of gaseous nitric oxide, comprising a water miscible organic compound capable of forming a reversible bond or association with nitric oxide. The common technical feature is not a special technical feature under PCT Rule 13.2 because it is disclosed in U.S. Patent No. 6,352,709 B1 to Stamler *et al.* (IDS dated 24 March 2006).

Furthermore, an undue burden on the Office exists if all the groups were searched because it would require different search fields that are non-coextensive with each other. A reference for alcohols herein would not necessarily be a reference for carbohydrates herein under 35 USC § 103 because the compounds are structurally different. Thus, an undue burden on the Office is seen for the search all inventions herein.

The requirement is still deemed proper and is therefore made FINAL.

Claims 42-51, 61-64, 67, 69, 71 and 73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5 March 2009.

Claims 53 and 57-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable

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generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5 March 2009.

Claims 41, 52, 55, 56, 65, 66, 68, 70, 72 and 74 will be examined on its merits herein.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41, 52, 55, 56, 65, 66, 68, 70, 72 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation “capable of forming a reversible bond or association with NO” in claims 41 and 52 render the claims herein indefinite. The recitation is not clearly defined in the specification, and therefore does not set forth the metes and bounds of the terms “capable of” and “association with”. Furthermore, the recitation does not convey a structural formula or chemical name to one of ordinary skill in the art. Although the recitation represents functional language and examples are provided in the instant Specification as to what compounds are represented by such a recitation, it is not clearly defined in the Specification. In the absence of a structural formula or chemical name, the claim is indefinite as one of ordinary skill in the art would not be apprised of the metes and bounds of the claimed invention. It is noted that the Specification indicates specific compounds that are “capable of forming a reversible

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bond or association with NO". Thus, it is respectfully suggested that Applicants incorporate these exemplary compounds or alcohols into their claim to render the claim definite.

The recitation "substantially no oxygen" in claims 70, 72 and 74 renders the claims herein indefinite. The Specification does not provide any guidance as to how "substantially" is defined. Therefore, in the absence of any teachings in the instant Specification, according to the Merriam-Webster OnLine dictionary (PTO-892, Ref. U), "substantially" is defined as "considerable in quantity" and "being largely but not wholly that which is specified." Thus, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "substantially no oxygen" herein.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 41, 52, 65, 66, 68, 70, 72 and 74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition for the delivery of gaseous nitric oxide (NO), comprising specific compounds capable of forming a reversible bond or association with NO, wherein said compound is a water miscible organic compound, comprising at least one hydroxyl group, does not

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reasonably provide enablement for a similar composition comprising any compounds capable of forming a reversible bond or association with NO, wherein said compound is a water miscible organic compound, comprising at least one hydroxyl group. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected invention is drawn to a composition for the delivery of gaseous nitric oxide, comprising a compound capable of forming a reversible bond or association with NO, wherein said compound is a water miscible organic compound, comprising at least one hydroxyl group.

Relative skill of those in the art: The relative skill of those in the art is high.

Breadth of claims: The claims are extremely broad in that they encompass any compound capable of forming a reversible bond or association with NO, wherein said compound is a water miscible organic compound and comprise at least one hydroxyl group.

Amount of guidance/Existence of working examples: The specification provides working examples in Table 1 of the instant Specification and includes different naturally occurring monosaccharides, specific amino acids, specific polyols, propanol, propanediol, amino-propanediol, ethanol, lactobionic acid, sucrose, polyethylene glycol, dextran, heparin, fucoidan and albumin, among several others.

Quantity of Experimentation Necessary: There exists an extensive list of compounds that meet that requirements of the claim limitations of being capable of forming a reversible bond or association with NO, wherein said compound is a water miscible organic compound and comprise at least one hydroxyl group. Even looking at one catalog alone, such as Sigma-Aldrich, one can identify hundreds, if not thousands, of compounds meeting this criteria. Thus, testing each of these compounds and their ability to deliver nitric oxide would require one to engage in undue experimentation.

State of the prior art/Predictability or unpredictability of the art: The skilled artisan would view that it is unlikely that one can predict whether all compounds that meet the requirements as claimed could be used to deliver nitric oxide. The specification discloses that proteins and carbohydrates can be used for delivery of nitric oxide. However, one skilled in the art would view that it is unlikely that all compounds meeting the limitations of the claim could be used. For example, ricin, a glycoprotein

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that has hydroxyl groups and can be dissolved in water, is highly toxic. Therefore, it is unlikely that one would use ricin as a delivery vehicle for treatment due to its toxicity. However, toxicity is relative and can also depend on concentration. Thus, compounds that are toxic at high concentration may not be toxic at low concentration and can be used as a vehicle for nitric oxide delivery when used in low concentration.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully describe the genus, visualize, or recognize, the identity of the members of the genus by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members of the genus herein, one of ordinary skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Genetech, 108 F.3d at 1366, states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Therefore, in view of the *Wands* factors as discussed above, e.g., breadth of claims, the amount of guidance provided and the predictability of the art, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Written Description

Claims 41, 52, 65, 66, 68, 70, 72 and 74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a composition for the delivery of gaseous nitric oxide (NO), comprising a compound capable of forming a reversible bond or association with NO, wherein said compound is a water miscible organic compound, comprising at least one hydroxyl group.

The MPEP states that for a generic claim, the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. See MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In

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Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618. Additionally, in *Carnegie Mellon University v. Hoffman-La Roche Inc.*, Nos. 07-1266, -1267 (Fed. Cir. Sept. 8, 2008), the Federal Circuit affirmed that a claim to a genus described in functional terms was not supported by the specification's disclosure of species that were not representative of the entire genus. Furthermore, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The claims are rejected under the written description requirement for failing to disclose a representative number of species for the claimed genus.

The Guidelines for Examination of Patent Applications under the 35 USC § 112, first paragraph, "Written Description" Requirement", published at Federal Register, Vol. 66, No. 4, pp. 1099-1111 outline the method of analysis of claims to determine whether adequate written description is present. The first step is to determine what the claim as a whole covers, i.e., discussion of the full scope of the claim. Second, the application should be fully reviewed to understand how applicant provides support for the claimed invention including each element and/or step, i.e., compare the scope of the claim with the scope of the description. Third, determine whether the applicant was in possession

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of the claimed invention as a whole at the time of filing. This should include the following considerations: (1) actual reduction to practice, (2) disclosure of drawings or structural chemical formulas, (3) sufficient relevant identifying characteristics such as complete structure, partial structure, physical and/or chemical properties and functional characteristics when coupled with a known or disclosed correlation between function and structure, (4) method of making the claimed invention, (5) level of skill and knowledge in the art and (6) predictability of the art. For claims 41, 52, 55, 56, 65, 66, 68, 70, 72 and 74, each of these factors has been considered, with the most relevant factors discussed below. For each claim drawn to a genus, each of these factors is to be considered to determine whether there is disclosure of a representative number of species that would lead one skilled in the art to conclude that applicant was in possession of the claimed invention. Where skill and knowledge in the art is high, adequate written description would require fewer species to be disclosed than in an art where little is known; further, more species would need to be disclosed to provide adequate written description for a highly variable genus.

First, what do the claims as a whole cover? Claims 41 and 52, and dependent therefrom, are directed to a composition for the delivery of gaseous nitric oxide (NO), comprising a compound capable of forming a reversible bond or association with NO, wherein said compound is a water miscible organic compound, comprising at least one hydroxyl group. Dependent claims 55 and 56 further limit the genus of the claimed compounds capable of forming a reversible bond or association with NO.

Second, how does the scope of the claims compare to the scope of the disclosure? The compounds claimed are broader than what is supported in the disclosure. The claims are drawn to any compounds that can form a reversible bond or association with NO and is a water miscible organic compound, but the disclosure only provides a very limited subset of species (and sub-genus) for such recited compounds.

Third, the factors need to be considered, with the most relevant factors discussed below.

Reduction to Practice: The compounds reduced to practice for the delivery of gaseous nitric oxide are disclosed in Table 1 of the instant Specification and include different naturally occurring monosaccharides, specific amino acids, specific polyols, propanol, propanediol, amino-propanediol, ethanol, lactobionic acid, sucrose, polyethylene glycol, dextran, heparin, fucoidan and albumin, among several others.

Disclosure of Drawings or Structural Chemical Formulas: The only disclosure, in addition to the species reduced to practice, is in the form of lists of possible compounds described using functional language, i.e., carbohydrates, proteins, peptides, alcohols. This type of disclosure is not viewed to be a representation of any of the species it encompasses. A “laundry list” disclosure of every possible species or sub-genus does not constitute a written description of every species in a genus because it would not “reasonably lead” those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F. 3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Therefore, there is no disclosure of species (e.g. by disclosure of structural/chemical formulae) in addition to those reduced to practice.

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does “little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate”. The CAFC further clearly states that “A definition by function, as we have previously indicated, does not suffice to define the genus...” at 1406 (emphases added).

Method of Making the Claimed Invention: The disclosure provides a general description as to how nitric oxide is infused into the carrier solutions. However, it is unclear whether such a method is applicable to the countless number of compounds that meet the claim limitations of being capable of forming a reversible bond or association with NO, wherein said compound is a water miscible organic compound and comprise at least one hydroxyl group, since each compound has a different solubility/miscibility in water.

Level of Skill in the Art and Knowledge in the Art: The level of skill in the art is high, about that of a Ph.D scientist with several years of experience.

Thus, having analyzed the claims with regard to the Written Description guidelines, it is clear that the specification does not disclose a representative number of species for the compounds that can form a reversible bond or association with NO and is a water miscible organic compound. Thus, one skilled in the art would be lead to conclude that Applicant was not in possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 41, 52, 55, 56, 65, 66, 68, 70, 72 and 74 are rejected under 35 U.S.C. 102(b) as being anticipated by Mailhes *et al.* (PTO-892, Ref. V).

Mailhes *et al.* disclose that 1,2-propanediol induces cytogenetic aberrations in mouse metaphase II oocytes that predispose zygotes to aneuploidy (abstract). Prior to use in i.p. injections, 1,2-propanediol is formulated in distilled water (p. 93, column 1, first full paragraph).

It is noted that Mailhes *et al.* do not indicate that the composition is capable of forming a reversible bond or association with NO, as instantly claimed. However, since products of identical chemical composition cannot have mutually exclusive properties, so long as the prior art discloses the same composition comprising the same ingredients as that instantly claimed, the limitations of the claim are deemed to have been met. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161.

Furthermore, in view of the pending rejection under 35 USC § 112, second paragraph, of claims 70, 72 and 74, it is considered that the disclosure of Mailhes *et al.* meets these claim limitations.

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Thus, the formulation of 1,2-propanediol in distilled water, disclosed by Mailhes *et al.*, anticipates claims 41, 52, 55, 56, 65, 66, 68, 70, 72 and 74.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. U.S. Patent No. 6,737,447 B1 to Smith *et al.* (PTO-892, Ref. A) teach nitric oxide-modified linear poly(ethyleneimine) fibers and their uses.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Supervisory Patent Examiner, Art Unit 1623

SCARLETT GOON
Examiner
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